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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,685	MODEL ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *2,23-30 and 32-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-22 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/27/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1, 3-22 and 31 in the reply filed on November 9, 2009 is acknowledged.

Claims 2, 23-30 and 32-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 9, 2009.

Claims 1, 3-22 and 31 are pending and will be examined.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on May 27, 2008 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 10-11, 16-17 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622). Wong teaches detection of promoter methylation in p16 in cancer (Abstract).

With regard to claim 1, Wong teaches a method for producing DNA, wherein a methylation analysis is used, comprising the steps of:

a) performing a genome-wide amplification (p. 2619, col. 2, where whole genome amplification was carried out with PEP amplification, p. 2620, col. 1), and b) using the amplificates generated in step a) as a standard in the methylation analysis (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction).

With regard to claim 3, Wong teaches an embodiment of claim 1 wherein the amplification methods performed are PEP, DOP-PCR or linker PCR (p. 2619, col. 2, where whole genome amplification was carried out with PEP amplification, p. 2620, col. 1).

With regard to claim 10, Wong teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by methylation- specific ligation methods, MSP, Heavy Methyl or MethyLight (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction, p. 2620. col. 1, where methylation specific PCR is described, see Figure 1).

With regard to claim 11, Wong teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by primer extension (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction, p. 2620. col. 1, where methylation specific PCR is described, see Figure 1).

With regard to claim 16, Wong teaches an embodiment of claim 1 wherein the methylation analysis is performed for the diagnosis of cancer diseases or other diseases associated with a modification of the methylation status (Abstract, Figure 1, Table 1, where the technique was used to detect methylation in cancer samples).

With regard to claim 17, Wong teaches an embodiment of claim 1 wherein the methylation analysis is performed for the prognosis of desired or undesired effects of drugs and for the differentiation of cell types or tissues, or for the investigation of the cell differentiation (Abstract, Figure 1, Table 1, where the technique was used to detect methylation in cancer samples).

With regard to claim 31, Wong teaches an embodiment of claim 1, wherein the genome-wide amplification is performed by exclusively using nucleotides or nucleotide triphosphates, respectively, which are non-methylated (p. 2620, col. 1, where the genome-wide amplification is carried out using non-methylated nucleotides).

Claims 18-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Adorjan et al. (Nucleic Acids Research, 2002, 30(5):e21, p. 1-9, IDS reference). Adorjan teaches microarray based DNA methylation analysis (Abstract).

With regard to claim 18, Adorjan teaches a method for the determination of methylation rates of DNA samples by means of microarrays containing CG and TG oligomers, comprising the steps of:

a) hybridizing the arrays with two calibration standards, which have defined methylation rates (p. 2, col. 2, where for each analyzed CpG position, CG and TG oligomers are spotted onto a glass array; Table 1, p. 3, col. 2, where DNA fragments of known methylation were mixed in different ratios and hybridized to the array, Figure 1);

b) using the hybridization values of step a) to determine a calibration curve for use as a suitable method of calculation (Figure 1, where the amount of methylation is calculated based on the hybridization and calibration on the array, see p. 3 col. 2); and

c) determining the actual methylation rates of the investigated DNA samples by using this prepared calibration curve (Figure 1, where the amount of methylation is calculated based on the hybridization and calibration on the array, see p. 3 col. 2).

With regard to claim 19, Adorjan teaches an embodiment of claim 18, wherein the two calibration standards have methylation rates of 0% and 100%, respectively (Figure 1, and legend, where the standards have methylation rates between 0 and 100%).

With regard to claim 20, Adorjan teaches an embodiment of claim 18, wherein more than two calibration standards are used, which have different methylation rates (Figure 1, and legend, where the standards have methylation rates between 0 and 100%).

With regard to claim 21, Adorjan teaches an embodiment of claim 18, wherein the actual methylation rates are determined in a multi-stage calculation process, comprising the steps of:
a) normalizing the hybridization values, wherein methylation signals are determined (p. 3, col. 1, where the statistical analysis is described, including the algorithms used, p. 3, col. 2, where the process of detecting and calibrating and normalizing the signals to correlate signals with degree of methylation, see Figure 1 and legend),
b) normalizing the methylation signals with the aim of variance stabilization (p. 3, col. 1, where the signals are normalized using a Support Vector Machine (SVM) and Sequential Minimal Optimization Algorithm, p. 3 col. 2, where the process of detecting and calibrating and normalizing the signals to correlate signals with degree of methylation, see Figure 1 and legend), and
c) determining the methylation rates by using the calibration standards and a suitable maximum likelihood algorithm (Figure 1, where the amount of methylation is calculated based on the hybridization and calibration on the array, see p. 3 col. 1-2, see above).

With regard to claim 22, Adorjan teaches an embodiment of claim 21, further comprising a step prior to step a) wherein the hybridization values are corrected for the background noise

inherent in the measurement method (p. 3, col. 1, where the signals are normalized using a Support Vector Machine (SVM) and Sequential Minimal Optimization Algorithm, p. 3 col. 2, where the process of detecting and calibrating and normalizing the signals to correlate signals with degree of methylation, see Figure 1 and legend).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 1, 4, 8-9, 11, 14-17 and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by Schatz et al. (Nucleic Acids Research 2004, 32(21):e165, p. 1-7). Schatz teaches methylation analysis using mass spectrometry analysis (Abstract).

With regard to claim 1, Schatz teaches a method for producing DNA, wherein a methylation analysis is used, comprising the steps of:
a) performing a genome-wide amplification (p. 1, col. 2 to p. 2, col. 1, where the unmethylated DNA amplified by MDA), and b) using the amplificates generated in step a) as a standard in the methylation analysis (p. 1, col. 2 to p. 2, col. 1, where the unmethylated DNA is mixed with methylated DNA for defined methylation states).

With regard to claim 4, Schatz teaches an embodiment of claim 1 wherein the amplification method performed is a multiple displacement amplification (MDA) (p. 1, col. 2, where unmethylated DNA was amplified using multiple displacement amplification).

With regard to claim 8, Schatz teaches an embodiment of claim 4, further comprising a commercially available DNA produced by MDA is used as a standard (p. 1, col. 2 to p. 2, col. 1, where the unmethylated DNA amplified by MDA is mixed with methylated DNA for defined methylation states).

With regard to claim 9, Schatz teaches an embodiment of claim 1 further comprising using restriction enzymes (p. 3, col. 2, where the DNA is restricted with restriction enzyme).

With regard to claim 11, Schatz teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by primer extension (Figure 1, where primer extension reactions were used to generate products which were used in RNAse T1 cleavage analysis of CpG methylation).

With regard to claim 14, Schatz teaches an embodiment of claim 1 wherein a mixture of methylated and non-methylated DNA is used as a standard (p. 1, col. 2 to p. 2, col. 1, where the unmethylated DNA amplified by MDA is mixed with methylated DNA for defined methylation states, p. 2, where the mixtures include 0, 20, 40, 50, 60, 80 and 100% methylation).

With regard to claim 15, Schatz teaches an embodiment of claim 1 wherein several mixtures of methylated and non-methylated DNA with different shares of methylated and non-methylated DNA are used as a standard (p. 1, col. 2 to p. 2, col. 1, where the unmethylated DNA amplified by MDA is mixed with methylated DNA for defined methylation states, p. 2, where the mixtures include 0, 20, 40, 50, 60, 80 and 100% methylation).

With regard to claim 16, Schatz teaches an embodiment of claim 1 wherein the methylation analysis is performed for the diagnosis of cancer diseases or other diseases

associated with a modification of the methylation status (Figure 3, where the methylation status in colon tumors were analyzed).

With regard to claim 17, Schatz teaches an embodiment of claim 1 wherein the methylation analysis is performed for the prognosis of desired or undesired effects of drugs and for the differentiation of cell types or tissues, or for the investigation of the cell differentiation (Figure 3, where the methylation status in colon tumors were analyzed).

With regard to claim 31, Schatz teaches an embodiment of claim 1, wherein the genome-wide amplification is performed by exclusively using nucleotides or nucleotide triphosphates, respectively, which are non-methylated (p. 1, col. 2, where unmethylated DNA was amplified using multiple displacement amplification).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17 and 31 above and further in view of Adorjan et al. (Nucleic Acids Research, 2002, 30(5):e21, p. 1-9).

Wong teaches all of the limitations of claims 1, 3, 10-11, 16-17 and 31. Wong does not teach the use of a microarray. Adorjan teaches microarray based DNA methylation analysis (Abstract).

With regard to claim 12, Adorjan teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by an amplification and a hybridization of the amplificates at oligomer microarrays (p. 2, col. 2, where for each analyzed CpG position, CG and TG oligomers are spotted onto a glass array; Table 1, p. 3, col. 2, where DNA fragments of known methylation were mixed in different ratios and hybridized to the array, Figure 1; see also p. 2, col. 2, where bisulfite conversion and amplification are discussed.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the analysis of methylation using microarrays as taught by Adorjan to arrive at the claimed invention with a reasonable expectation for success. As taught by Adorjan, "We have developed the first microarray-based technique which allows genome-wide assessment of selected CpG dinucleotides as well as quantification of methylation at each site. Several hundred CpG sites were screened in 76 samples from four different human tumour types and corresponding healthy controls. Discriminative CpG dinucleotides were identified for different tissue type distinctions and used to predict the tumour class of as yet unknown samples with high accuracy using machine learning techniques". Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the analysis of methylation using microarrays as taught by Adorjan to arrive at the claimed invention with a reasonable expectation for success.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17 and 31 above and further in view of Tost et al. (Nucleic Acids Research, 2003, 31(9):e50, p. 1-10).

With regard to claim 13, Tost teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by means of a multiplex PCR (p. 6, col. 2, where the CpG methylation was detected using multiplex primer extension).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the analysis of methylation using multiplex amplification as taught by Tost to arrive at the claimed invention with a reasonable expectation for success. As taught by Tost, "Calibration curves were recorded for simplex, duplex and triplex analysis. For multiplex analysis only extension primers were chosen that did not overlap in their sequence". Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the analysis of methylation using multiplex amplification as taught by Tost to arrive at the claimed invention with a reasonable expectation for success.

Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schatz et al. (Nucleic Acids Research 2004, 32(21):e165, p. 1-7) as applied to claims 1, 4, 8-9, 11, 14-17 and 31 above and further in view of Apgar et al. (Human Immunology, 2003, 64(10), Suppl. 1, p.

S86, Abstract). Schatz teaches methylation analysis using mass spectrometry analysis (Abstract).

With regard to claim 5, Apgar teaches an embodiment of claim 4, further comprising using a phi 29 polymerase (Abstract, line 5).

With regard to claim 6, Apgar teaches an embodiment of claim 4, further comprising using a commercially available kit (Abstract, line 10).

With regard to claim 7, Apgar teaches an embodiment of claim 6, wherein the commercially available kits are "GenomiPhi" (Amersham Biosciences) or "Repli-g" (Molecular Staging) (Abstract, line 10).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Schatz to include the GenomiPhi kit of Apgar to arrive at the claimed invention with a reasonable expectation for success. As taught by Apgar, "replicate aliquots of dilute DNA were amplified by MDA using a GenomiPhi kit" (Abstract, line 10). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Schatz to include the GenomiPhi kit of Apgar to arrive at the claimed invention with a reasonable expectation for success.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Dean et al. (US Patent 6,617,137 September 2003) teaches methods of whole genome amplification.

Conclusion

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Examiner, Art Unit 1637

SKM